REMARKS

I. Introduction

Claims 65, 67, 81, 101-110, and 116-143 are pending in the instant application. Claim 131 has been amended according to the Examiner's suggestion to properly depend from claim 127. Claim 81 has been amended to recite the term "exactly." Applicants reserve the right to pursue the nonelected and/or canceled subject matter in related applications, such as divisional applications.

II. The rejection of claims 65, 67, 101, 119, 120, 139, and 141 under 35 USC §102(b) should be withdrawn.

In paragraph 2 of the Office action, the Examiner rejected claims 65, 67, 101, 119, 120, 139, and 141 under 35 USC §102(b) as being anticipated by Gregori *et al.* The Applicants respectfully traverse.

The Examiner alleged that Gregori *et al.* disclose a self aggregation domain of amyloid beta protein comprising the substitution of amino acid 40 with a cysteine residue having a reactable side chain and further modified with a metal ion (gold). The Examiner further alleged, "Gregori *et al.* further disclose that the labeled peptide forms ordered aggregates see col 1 of page 60, therefore one of ordinary skill would expect that the gold labeled side chain is exposed to the environment in an ordered aggregate because gold does not appear to inhibit aggregation as would be expected if the gold was buried in the interior of the aggregate."

As explained by Dr. Susan Lindquist in a rule 132 Declaration filed herewith (hereinafter "the Lindquist Declaration") Gregori et al. do not teach that the labeled peptide forms ordered aggregates as alleged by the Examiner. (See, e.g., paragraphs 2.2-2.6 of Lindquist Declaration) Rather, Gregori et al. indicates that the Nanogold moiety binds to a single Aβ peptide that does not aggregate. for example, Dr. Lindquist explains that the migration patterns of unlabeled Aβ peptide (~6 kDa) and the free Nanogold (~14 kDa) in lanes 1 and 3, respectively, of figure 2A, indicated that Nanogold-labeled Aβ behaved as a monomer form of Aβ (Figure 2A, lane 2; total MW of ~17-21 kDa). (Lindquist Declaration at 2.3-2.4.) Aggregated Aβ

would be expected to have a much higher molecular weight. (Lindquist Declaration at 2.4)

Not only does Gregori et al. teach that labeled Aβ peptides do not aggregate, the Lindquist Declaration explains why scientists skilled in the art would not expect to observe aggregation of labeled Aβ peptides. (Lindquist Declaration at 2.9.) Briefly, the Nanogold moiety is quite large in proportion to the Aβ peptide, and would be expected to prevent the formation of higher ordered aggregates due to steric hindrance. (In other words, spatial constraints due to the conjugated label would be expected to prevent the natural protein-protein interactions from occurring.)

Claim 65 recites the limitation of "...wherein polypeptides comprising the SCHAG amino acid sequence are capable of forming ordered aggregates;..." Similarly, claim 67 recites "A polymer comprising polypeptide subunits coalesced into ordered aggregates,..." Gregori et al fails to teach that labeled Aβ peptides form ordered aggregates, let alone any mention of polymers. (Lindquist Declaration at 2.10.) Accordingly, the rejection of claims 65 and 67 as anticipated over Gregori et al. should be withdrawn.

Claim 101 recites that the substituted amino acid is exposed to the environment in an ordered aggregate comprised of the polypeptide. However, as explained above, such aggregates are not described in Gregori *et al.*, and consequently, there is no basis for alleging or inferring that Gregori *et al.* teaches a polypeptide that satisfies claim 101.

Claims 119 and 141 recite the limitation that the SCHAG amino acid sequence comprises a prion-aggregation domain. (See also specification at page 9, lines 21-24 for definition.) Claims 120 and 139 recite the limitation of "A filamentous polymer" or "A fibrous polymer," respectively. As described above, Gregori et al. teaches the interaction between a labeled Aβ peptide with the eukaryotic proteasome. There is absolutely no mention in Gregori et al. of prion-aggregation domains. The protein interaction described by Gregori et al. involves a labeled Aβ peptide and the eukaryotic proteasome which has nothing whatsoever to do with self-aggregation of a prion protein. Likewise, the Aβ-proteasome interaction was not reported to produce fibrous or filamentous polymers. Indeed, the Aβ -proteasome interaction is so far removed from the self-aggregation interaction described in the

instant application for SCHAG polypeptides that one of ordinary skill in the art would not expect Aβ -proteasome complexes to form filamentous or fibrous polymers. Accordingly, the rejection of claims 119, 120, 139, and 141 as anticipated over Gregori et al. should be withdrawn.

III. The rejection of claim 81 under 35 USC §102(b) should be withdrawn.

In paragraph 3 of the Office Action the Examiner rejected claim 81 under 35 USC §102(b) as being anticipated by Paushkin *et al.* The Examiner alleged that Paushkin *et al.* discloses the NM fragment of yeast Sup35, which allegedly (naturally) has multiple reactive residues. The Examiner further alleges that the Applicant's amendment to claim 81 does not require that there be exactly two selectively reactive side chains.

In response, claim 81 has been amended to add the term "exactly" preceding "two amino acid residues having selectively reactive amino acid side chains that are exposed to the environment and serve as selectively reactive sites in ordered aggregates of the polypeptide." Thus, the Examiner's assertion that "the claims do not require that there be exactly two selectively reactive side chains" is moot. Moreover, Paushkin *et al.* teaches only the native NM region of Sup35 and neither discloses nor suggests the desirability or advantages to modifying the sequence to include exactly two, selectively reactive sites at which separate modifications can be introduced. Thus, the rejection should be withdrawn.

IV. The rejection of claims 102-110, 116, 119-122, 124-126, 132, 134, 135, 137-140, 142, and 143 under 35 USC §103(a) should be withdrawn.

In paragraph 5 of the Office Action, the Examiner rejected claims 102-110, 116, 119-122, 124-126, 132, 134, 135, 137-140, 142, and 143 under 35 U.S.C. §103(a) as allegedly unpatentable over King *et al.* in view of Gregori *et al.*

At the outset, the Applicants maintain their position that one of ordinary skill in the art would not have been motivated to look beyond King et al. to find assays to monitor the aggregation of the prion-aggregation domain of prion proteins. Nonetheless, even if one had been motivated to look for new techniques for monitoring prion-like aggregation, there would have been no motivation to look to Gregori *et al.* As explained above in Section II and in the Lindquist Declaration,

Gregori *et al.* does *not* teach monitoring prion-like aggregation, and does *not* report that the cysteine-modified, gold labeled amyloid beta self-aggregated. Instead, the available data reported indicated that such aggregation did *not* occur. (Lindquist Declaration at 2.2-2.6.) Gregori *et al.* teach an alleged 1:1 or 2:1 binding (*not higher ordered aggregates*) between two different proteins (*not self-coalescing*), amyloid-beta and the 20S proteasome. (Lindquist Declaration at 2.3-2.4.) Each of the rejected claims recites or depends from a claim which recites that the polypeptides are present in (or form) ordered aggregates. For these and other reasons, the rejection of claims 102-110, 116, 119-122, 124-126, 132, 134, 135, 137-140, 142, and 143 based on King *et al.* and Gregori *et al.* under 35 §U.S.C 103(a) should be withdrawn.

V. The rejection of claims 65, 67, 81, 101-110, 116, 119-126, 127-131, and 119-141 under 35 USC §103(a) should be withdrawn.

In paragraph 6 of the Office Action, the Examiner rejected claims 65, 67, 81, 101, 119, 120, and 139-141 under 35 §U.S.C 103(a) as being unpatentable over U.S. Patent No: 5,750,361 (hereinafter "the Prusiner patent") in view of Stayton *et al.* In paragraph 7 of the Office Action, claims 102-109, 116, 121-126, and 132 were rejected by the Examiner as being unpatentable over the Prusiner patent in view of Stayton *et al.* and in further view of King *et al.* In paragraph 8 of the Office Action, the Examiner rejected claims 127-131 and 133-138 as being unpatentable over the Prusiner patent in view of Stayton *et al.* and King *et al.*, and in further view of Paushkin et al. The applicants respectfully traverse.

As explained in detail by Dr. Lindquist in her Declaration filed herewith, there would have been no motivation to combine the teachings of the Prusiner patent with Stayton *et al.* (Lindquist Declaration at 3.6-3.14.) Prusiner concerns screening for compounds which inhibit prion complex formation, and a person of ordinary skill who was considering modification of Prusiner would have been considering Prusiner in this context, and looking for improvements that were rapid, inexpensive, cost-effective, and predictive of prion behavior *in vivo*. As Dr. Lindquist explains, a person of ordinary skill would not have combined Stayton *et al.* with Prusiner because the teachings in Stayton *et al.* would have been considered slow, difficult, expensive, and les predictive of prion behavior *in vivo*. (Lindquist Declaration at 3.9-3.10.)

The Examiner asserts that the motivation to combine Prusiner and Stayton et al. "... was provided by U.S. Patent No: 5750361 wherein it is stated that the polypeptide should be modified as described in the art and that amino acids could be substituted as long as the change does not effect complex formation..." (See Office Action at page 10) The Applicants emphasize that the Prusiner patent was concerned with the identification of inhibitors of prion complex formation and teaches a complex-inhibition assay that can be practiced with unmodified PrP protein sequences. Further, the labeling techniques taught in the Prusiner patent do not alter the PrP primary structure. One of ordinary skill in the art would not have been motivated to seek techniques in the art that would alter the native PrP sequence (as taught by Stayton et al.) because doing so would compromise the predictability of the complex-inhibition assay.

Moreover, even if there had been motivation to combine the references, Stayton *et al.* fails to teach a technique that one of ordinary skill in the art could have used successfully to study the SCHAG polypeptides described in the instant application. (Lindquist Declaration at 3.3-3.5.) The techniques employed by Stayton et al. relied upon the availability of the crystal structure of Cytochrome b5 to analyze the structure of the protein. (See, e.g., Stayton *et al.* at page 13545 and Figure 1) One of ordinary skill in the art would have recognized that such structural data was neither available nor obtainable for SCHAG proteins, which form fibers. (Lindquist Declaration at 3.4.) Further, even if such detailed structural data were available, a person of ordinary skill in the art would recognize that any structural information obtained from a SCHAG polypeptide in a theoretical crystalline state would not represent the SCHAG polypeptide in its natural, soluble state or its fiber-forming state. As such, any structural data obtained on a SCHAG sequence according to the method of Stayton *et al.* would not assist the selection of potential amino acid residues with reactable side chains that are exposed to the environment. (Lindquist Declaration at 3.5.)

In view of the foregoing remarks, the rejection of claims 65, 67, 81, 101-110, 116, 119-126, 127-131, and 119-141 under 35 USC §103(a) as being unpatentable over the prior art should be withdrawn.

VI. The rejection of claim 131 under 35 USC §112, second paragraph, should be withdrawn.

In paragraph 10 of the Office Action, the Examiner rejected claim 131 under 35 USC §112, second paragraph, as being indefinite because claim 131 improperly depended from itself. The Applicants have amended claim 131 to properly depend from claim 127 as suggested by the Examiner. Thus, the rejection of claim 131 under 35 USC §112, second paragraph, should be withdrawn.

VII. The rejection of claims 124, 127-131, and 134-137 under 35 USC §112, first paragraph, should be withdrawn.

In paragraph 12 of the Office Action, the Examiner rejected claims 124, 127-131, and 134-137 under 35 USC §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleged that "the claims require an essentially limitless number of polypeptides having only a 90% identity with SEQ ID NO: 2..." (Page 17, paragraph 12 of the Office Action) The Applicants respectfully traverse.

First, the scope of claims 124, 127-131, and 134-137 is more limited than alleged by the Examiner. For example, each of the above claims is limited to polypeptide(s) that "...self coalesces into higher ordered aggregates." Thus, in addition to sequence similarity, the claimed polypeptides must also possess a specific activity. The specification as originally filed teaches:

> [From the term "self-coalesces," it will be understood that a SCHAG amino acid sequence may be expected to coalesce with identical polypeptides and also with polypeptides having high similarity (e.g., less than 10% sequence divergence) but less than complete identity in the SCHAG sequence.] (page 6, lines 19-22)

Second, the specification as originally filed teaches assays to select functional (i.e. polypeptides that retain the ability of self-coalescence, etc.) polypeptides. For example, Example 9, section B teaches a variety of cysteine-substituted mutants of the NM region of Sup35p and biochemical and biophysical techniques to determine their viability (i.e., their expression levels in bacteria, secondary structure measured by circular dichroism, fiber assembly by Congo red binding, and fiber morphology by electron microscopy). Thus, not only does the specification as originally filed teach specific SCHAG amino sequences and how to

make variants, the specification also teaches the appropriate assays to determine which SCHAG variants that maintain the ability to self coalesce.

Recitation of percent identity, in combination with a functional limitation to a genus, is an accepted method of describing and claiming a genus of biomolecules. Example 14 of the Revised Interim Written Description Guidelines Training Materials explains that a claim that recites a percent identity to a specific SEQ ID NO in combination with a specific biological activity meets the requirements of 35 USC §112, first paragraph because all members have a specified percent identity to the reference compound and also because all of the variants possess the specified activity. As discussed above, claims 124, 127-131, and 134-137 of the instant application are limited to polypeptide(s) that "...self coalesces into higher ordered aggregates."

In view of the foregoing remarks, the rejection of claims 124,127-131, and 134-137 under 35 USC §112, first paragraph, should be withdrawn.

CONCLUSION

For the foregoing reasons, reconsideration and withdrawal of all rejections and objections is requested. However, if the Examiner has questions, or identifies any remaining issues preventing allowance that might be resolved by a telephonic interview or examiner's amendment, the Applicants request and invite the examiner to telephone the undersigned attorney to resolve such questions or issues.

Respectfully submitted,

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